Peer Review
Experimental Toxicology Division
NHEERL

# Susceptibility Factors for the Development of Allergic Lung Disease and Asthma

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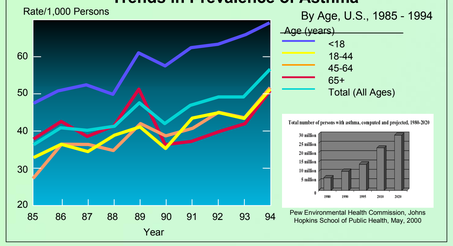
SUSCEPTIBILITY, ALLERGY & ASTHMA

## Introduction

More than 17 million people in the U.S. have asthma and this figure is estimated to increase over the next 20 years. It is thought that this increase is due to lifestyle changes such as reduced exercise and changes in diet as well as undefined changes in the environment. The objective of this research program is to understand which host factors and environmental exposures contribute to increased prevalence of allergic sensitization which is a precursor for the development of asthma.

### Trends in Prevalence of Asthma




### Why the increase?

Pesticides?

Vaccination and infection rates?

Air Pollution?

Diet?

Reduced exercise and time indoors?

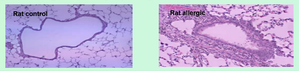
## Methods and Approach

### Allergic Sensitization Paradigm in Brown Norway Rats

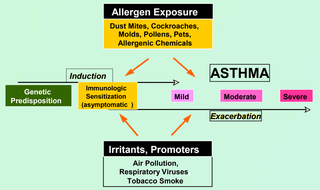
BN rats can become sensitized to house dust mite and produce IgE antibody and Th2 cytokines.

After allergen challenge, rats exhibit immediate and late phase responses, eosinophil infiltration and airway hyperresponsiveness to methacholine.

Adoptive transfer experiments show that the pathophysiological aspects of the disease state are mediated by immune components including serum IgE and T lymphocytes




### Exogenous factors in the pathogenesis of asthma




## Aims

Determine whether pre-exposure to the vaccine component (*B. pertussis*) affects mucosal sensitization to house dust mite.

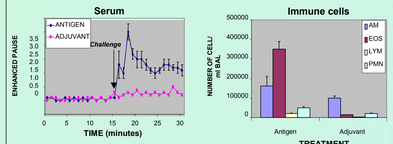
Assess the effect of food restriction on allergic sensitization in Brown Norway rats.

Investigate the effect of oil fly ash exposure on either the sensitization or challenge phase in an animal model of asthma

Investigate the mechanisms by which air pollutants may act as adjuvants to enhance allergic lung disease.

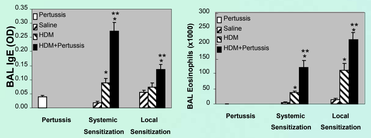
## Results

### Immediate Airway Responses and Pulmonary Eosinophilia are Increased in BN Rats Injected with Sera or Cells From Sensitized Animals



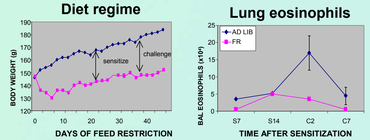

*Lambert et al, Am J Resp Crit Care Med. 157, 1998*

### Pertussis immunized rats have higher IgE and higher pulmonary eosinophils



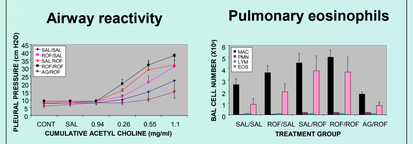

*Dong et al, Tox Sci. 72: p113, 2003*

### Food restricted rats have less clinical indicators of asthma



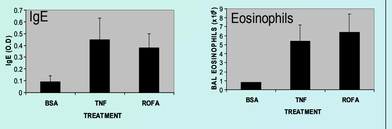

*Dong et al, Env Hlth Perspec, 108: p1125, 2000*

### Rats exposed to combustion pollutants sensitize more readily to house dust mite and have stronger responses after a challenge exposure



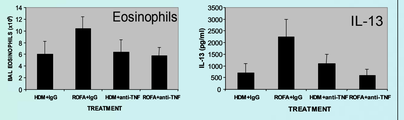

*Gilmour et al, Env Hlth Perspec, 109: p619, 2001*

### TNF-α produces as much adjuvant effect as residual oil fly ash




*Lambert et al, Exp Lung Res 27:p617, 2001*

### Treatment with anti TNF-α reduces adjuvant effect of ROFA to control (allergic) levels




*Lambert et al, Exp Lung Res 27: p617, 2001*

## Conclusions

The Brown Norway rat model of respiratory hypersensitivity to house dust mite displays many of the same clinical features as allergic asthma.

Systemic injection with the vaccine component B pertussis enhances mucosal allergic sensitization to HDM in weanling rats illustrating the possibility that immunizations may promote atopic disease.

Food restriction enhances host defenses and increases anti-oxidant status but also renders animals non-responsive to allergen sensitization and challenge.

Exposure to combustion air pollutants such as ROFA or its associated metals increases allergic sensitization and can also increase the severity of lung disease at challenge.

Treatment with the pro-inflammatory cytokine can mimick the adjuvant properties of air pollutants while neutralization of this mediator can negate the increased sensitization caused by exposure to ROFA.

## Impact

The development of animal models of respiratory hypersensitivity enable us to determine which host and environmental factors play a role in enhancing the risk of developing asthma or in exacerbating pre-existing disease. The understanding of these responses in whole animals and in human and rodent cells will allow extrapolation of health effects to humans, and will provide a data base for the risk assessment of individual and mixed air pollutant atmospheres.

## Future Directions

Examine the ability of diesel emissions from a variety of different engines and operating conditions to enhance allergic sensitization or exacerbate challenge responses.

Identify signal transduction mechanisms associated with increased allergic immune responses

Correlate signaling and mediator production between animal and human epithelial cells, macrophages lymphocytes and dendritic cells following exposure to diesel

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